Correlations between the Mucus Symptoms and the Hormonal Markers of Fertility throughout Reproductive Life

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Introduction

The primary aims of the present study were firstly to test the accuracy of the self-observed mucus symptoms in identifying the fertile and infertile phases of the ovarian cycle as used in the Ovulation Method (Billings), secondly to assess whether a do-it-yourself kit for measuring urinary oestrogen and pregnanediol excretion would be of value in natural family planning (NFP), thirdly to document ovarian activity under all possible conditions encountered in a large population of women, and fourthly, to feed back this information for the improvement of methods of NFP.

For the purposes of NFP, the ovulatory cycle can be divided into four phases. The first is the bleeding phase, which is the most obvious to the woman and is used for defining the beginning and the end of the cycle; this phase need not necessarily be "safe" because in short cycles bleeding may precede ovulation by only a brief time-interval. The second constitutes the early "safe" days, which occupy a variable interval of time, being prolonged for many weeks in very long cycles and being absent in very short cycles. The third phase is the fertile period during which conception from an act of intercourse is possible; during this time the chances of conception increase from practically zero at the beginning to a maximum of 40–50% 6–12 hours before ovulation and then drop rapidly to reach zero again 24–48 hours after ovulation. The duration of the fertile phase depends on the fertility of the couple, being up to 7 days for the highly fertile, 4–5 days for the average couple and only several hours for the relatively infertile couple. The fourth phase comprises the late safe days of the luteal phase, which begin 2–3 days after ovulation and last for the remaining 10–14 days of the cycle.

Ovulation is the central event in the fertile cycle. Several markers are available for identifying this event. Those we have used have been the mid-cycle peaks of luteinizing hormone (LH) and follicle stimulating hormone (FSH) as measured in serum and in urine by radioimmunoassay, the mid-cycle peak of oestrogen excretion in urine measured by fluorimetry (Brown *et al.* 1968) and the rise in urinary pregnanediol excretion measured by gas–liquid chromatography (Barrett and Brown 1970) and, more recently, visualization of the follicle by ultrasound. The women recorded their cervical mucus symptoms according to the rules of the Ovulation Method (Billings *et al.* 1980; Billings and Westmore 1980). The last day of fertile-type mucus ("peak" day) and the rise in body basal temperature (BBT) were also recorded.

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The scores for cervical mucus gradings are shown in Table 1. The rise in BBT was defined as the day on which the basal temperature permanently exceeded for that cycle a marginal line drawn above the maximum values of the follicular phase for the subject.

For NFP, the other important event is the beginning of the fertile phase. Unlike ovulation, this is not a fixed point but depends on the fertility of the couple. We have used the first rise in oestrogen production observed during the cycle and the first change in mucus from the basic infertile pattern of the early safe days (if present) as the markers for the beginning of the fertile phase.

Table 1. Cervical mucus grading showing the numerical score according to the appearance of the mucus

	−1	Dry sensation
	Definite change	
Infertile	1	Not dry, nothing seen
Infertile	2	Yellow or white — minimal
Infertile	3	Yellow or white — sticky
Possibly fertile	4	Cloudy, becoming clearer; sticky
	Definite change	
Fertile	5	Thinner, more stretchy
Fertile	7	Stretchy, lubricative, clear (may be cloudy)
Fertile	9	Wet, slippery — variable amount

Correlations between the Mid-cycle Markers of Ovulation

Table 2 shows the days on which the above mid-cycle events occurred in 23 normal ovulatory menstrual cycles defined by the finding of a mid-cycle peak of both serum LH and urinary oestrogen and a luteal phase rise of urinary pregnanediol exceeding 2 mg/24 hours. All events are numbered relative to the day of the mid-cycle serum LH peak = day 0, which was unambiguously defined in all cycles. The LH surge is the trigger for ovulation and therefore the LH peak is considered to be the most accurate hormonal marker of ovulation; it occurs approximately on the day before ovulation. The mid-cycle peak of FSH in serum corresponded almost exactly with the serum LH peak in most of the cycles studied, and this also applied to the FSH peak in urine. The urine LH peak showed a poorer correlation, and multiple peaks were observed in seven cycles; a single urine LH peak was observed on the same day as the serum LH peak in 12 cycles, on the day before in three cycles, and on the day after in one cycle. A well-defined oestrogen peak was observed on the same day as the serum LH peak in 11 cycles, on the day before in seven cycles and 2 days before in one cycle. A double peak was observed in one cycle. It was of interest that in eight of the nine cycles in which an oestrogen peak was observed preceding the serum LH peak, peaks were also observed in urinary LH and/or FSH which also preceded the serum LH peak. This association was statistically significant and showed that the observed serum LH peak could have occurred on the day after the true LH peak in approximately 30% of cycles. This discrepancy in timing is probably due to the marked fluctuations in the serum LH values caused by episodic secretion of the hormone by the pituitary.

Table 2. Mid-cycle events relative to the serum LH peak in 18 parous and five nulliparous women aged 23–39 years (mean 30 years)

Cycle lengths were 24–33 days (mean 27 days). Some events showed multiple peaks; in these cases an asterisk denotes the highest peak

Subject No.	Luteal phase length (days)	Days relative to serum LH peak = day 0						
		Serum FSH peak	Urine				Basal temp. rise	Last day 'fertile' mucus
			LH peak	FSH peak	Oestrogen peak	Pregnanediol rise		
1	13	0	0	0	0	+2	+2	+1
2	12	0	−1, +1, +3*	−1	0	+1	+1	+1
3	14	0	−1	−1	−2	0	+2	0
4	14	+1	0	0	0	+2	+4	+1
5	13	0	−1, +1, +3*	−1	−1	+1	0	+1
6	15	0	+1	+1	0	+2	+2	+1
7	14	0	0	0	−1	+2		+1
8	12	0	0	0		+3	+1	0
9	15	0	−2*, 0		−1	+1	+2	0
10	15	0	0	0	0	+2	+2	0
11	16	0, +1	−1, +2*	−1	−1	+2	+3	+1
12	15	0	−1, +2*	−1, +2*	−1	+1	+2	+1
13	13	0	0	0	0	0	+4	0
14	14	0	0	0	0	0	+2	0
15	13	0	0	−1	−1	+1	+2	−1
16	14	0	−1, +2*	0	0	0	+2	+1
17	14	0	0	0	0	+2	+3	+1
18	16	0	−1, +1*	+1	−1	+1	+2	+3
19	14	0	−1	−1	−2, +1*	+2	+3	0
20	15	0	0	−1	0	+2		
21	14	+1	0	0		+2	+3	
22	14		−1	−1		+2	+2	
23	13	0	0		0	+1	+4	
Mean	14·0	+0·1	+0·15	−0·26	−0·48	+1·4	+2·2	+0·6
Range	12 to 16	0 to +1	−2 to +3	−1 to +2	−2 to +1	0 to +3	0 to +4	−1 to +3

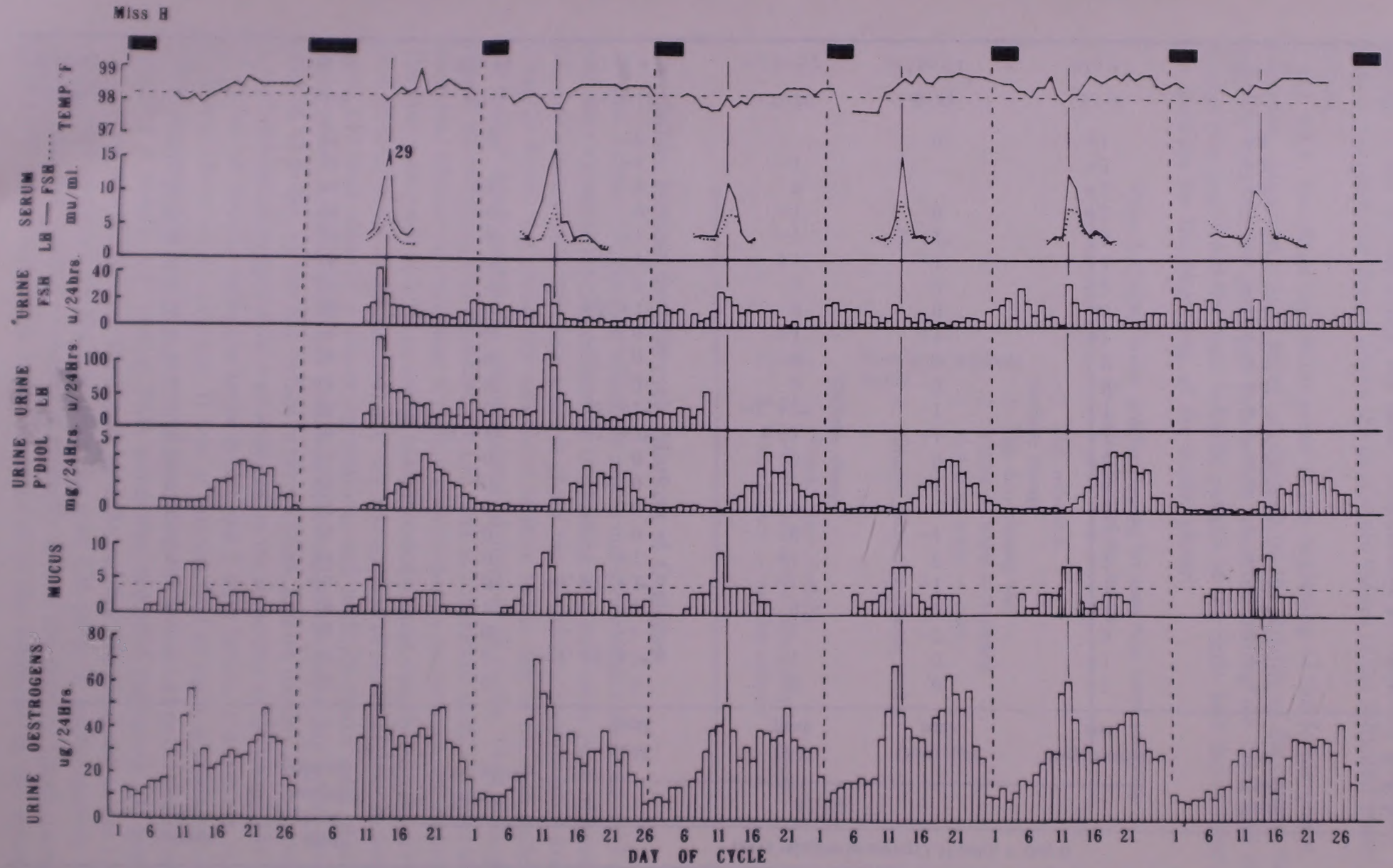

Figure 1. Daily urinary oestrogen and pregnanediol values, mucus scores, urine LH and FSH, serum LH and FSH and BBT in seven cycles contributed by the one individual (Miss H). Vertical solid lines are the days of the serum LH peaks, vertical dotted lines are the first days of bleeding, horizontal dotted lines represent the transition from infertile or possibly fertile-type mucus to fertile-type mucus and the marginal line for BBT. In this and all subsequent figures ▬ = bleeding.

The relationships between the mid-cycle markers are also illustrated in Figure 1, which shows the values obtained for urine oestrogens, the mucus symptoms, urine pregnanediol, urine LH and FSH, serum LH and FSH, and basal body temperature plotted over seven cycles contributed by the one individual (Miss H). The solid vertical lines represent the day of the serum LH peak. It is seen, for example, in the second and third cycles that the peaks of oestrogen and mucus scoring and of urine LH and FSH all preceded those of serum LH and FSH by 1 or 2 days. In cycle 6 all markers coincided.

Figure 2 summarizes in graphical form the data shown in Table 2. The cumulative percentage of cycles in which a particular mid-cycle event had occurred by a particular day are plotted relative to the day of the serum LH peak = day 0. For exact correspondence with the serum LH peak, a vertical line would be shown on day 0, as

CORRELATION BETWEEN SERUM AND URINE LH AND FSH PEAKS, URINE OESTROGEN PEAK, PREGNANEDIOL RISE, LAST DAY OF 'FERTILE' MUCUS AND B.B.T. RISE IN 23 CYCLES

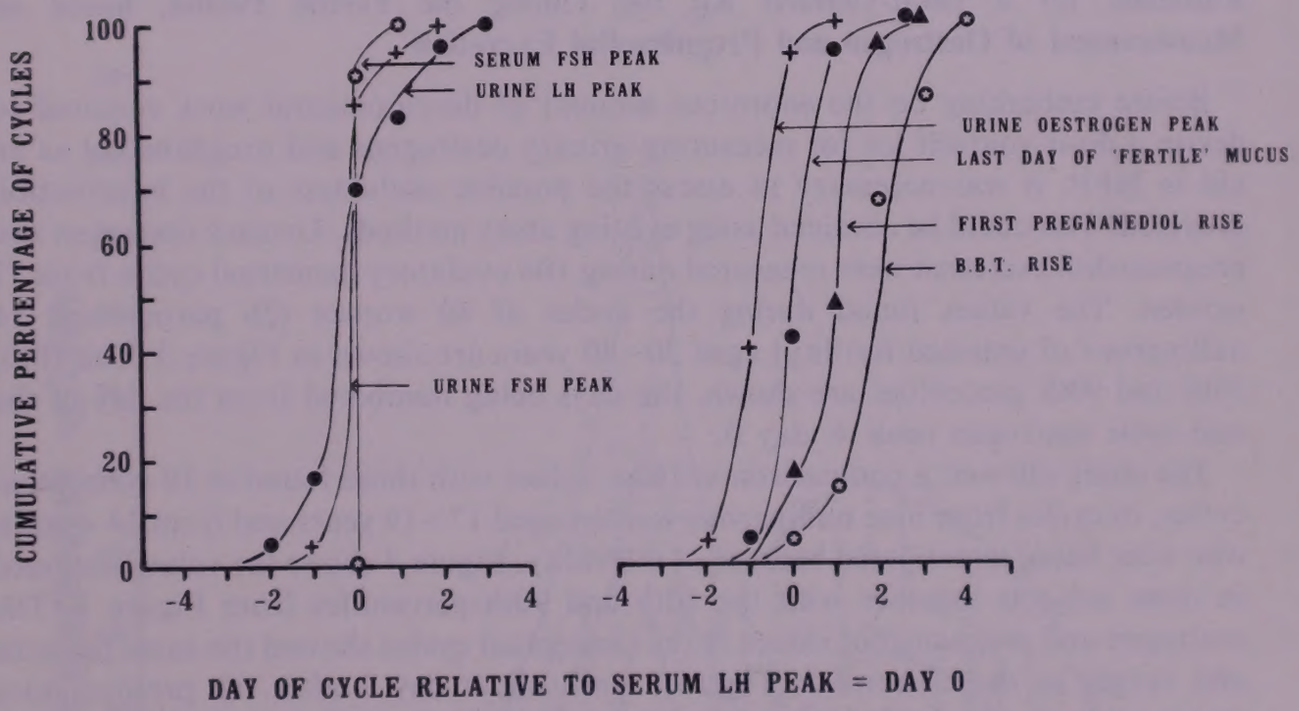

Figure 2. Cumulative percentage of cycles in which the events shown in Table 2 had occurred by a particular day. Days are numbered from the day of the mid-cycle serum LH peak = day 0, which itself occurs within ±1 day of the peak secretion of LH by the pituitary.

was almost the case for the serum FSH peak. The flatter the S-shaped curve, the poorer the correspondence. Thus, the urine oestrogen peak had occurred by day −2 in 5% of cycles, by day −1 in 40% of cycles, by day 0 in 95% of cycles and by day +1 in 100% of cycles. It is seen that the rise in BBT showed the flattest curve and therefore the poorest relationship to the serum LH peak.

When it is considered that the serum LH peak, as determined by daily sampling, may be in error by 1 day, it is seen from Figure 2 that no one of the eight assessments

applied was an absolute marker for timing ovulation. The mucus symptoms were as accurate as the urinary oestrogen peak and more accurate than the rises in pregnanediol or BBT; it is possible that they were as accurate as the serum LH peak itself. More accurate definitions of the LH peak would be provided by frequent multiple sampling over the days of the peak. Other workers are attempting to correlate the moment of the serum LH peak with the moment of ovulation as determined by direct visualization of the ovaries, and are finding a mean time interval between the two events of 17 hours. However, there is a wide scatter of results, and, from our work, it would appear that the peak is relatively unimportant; the event which is important is the level of LH required to initiate rupture of the follicle (ovulation). This critical level is reached before the peak value and ovulation occurs almost precisely 37 hours later. This is the time interval between giving one dose of human chorionic gonadotrophin (HCG), which provides the LH surge, in one bolus, and ovulation. As the accurate timing of ovulation to within a 24-hour period presents considerable difficulties, it should be realized that any dating of ovulation used in the present study has a range of probability which extends at least over two 24-hour periods.

Rationale for a Do-it-yourself Kit for Timing the Fertile Period, based on Measurement of Oestrogen and Pregnanediol Excretion

Before embarking on the enormous amount of developmental work required to devise a do-it-yourself kit for measuring urinary oestrogens and pregnanediol as an aid in NFP, it was necessary to assess the possible usefulness of the information provided. This could be obtained using existing assay methods. Urinary oestrogen and pregnanediol excretion were measured during 104 ovulatory menstrual cycles from 77 women. The values found during the cycles of 40 women (26 parous and 14 nulliparous of untested fertility) aged 20–40 years are shown in Figure 3. The 10th, 50th and 90th percentiles are shown, the days being numbered from the day of the mid-cycle oestrogen peak = day 0.

The study allowed a comparison of these values with those found in 10 conceptual cycles, in cycles from nine nulliparous women aged 17–19 years and from 24 women who were being investigated because of infertility. Figure 4 shows the values obtained in these subjects together with the 10th and 90th percentiles from Figure 3. The oestrogen and pregnanediol values in the conceptual cycles showed the same patterns and ranges as those shown in Figure 3 until about day 7 after the pre-ovulatory oestrogen peak. As the facility for conception is an obvious requirement of a normal cycle, it can be concluded that the values shown in Figure 3 for the 40 women aged 20–40 years are also representative of normal fertile cycles. It can also be concluded that the relative infertility of the human is not due to a high percentage of abnormal cycles as judged by hormone assays. The values in the teenagers (Figure 4) were generally lower than those found in the older women and this was statistically significant on the day of the oestrogen peak. The luteal phases in the normal women (Figure 3), as calculated from the pre-ovulatory oestrogen peak to onset of bleeding, ranged from 11 to 17 days (mean 13·6 days). Two of the teenagers had short luteal phases of 9 and 10 days. Our studies show that such short luteal phases are a definite bar to fertility and are more important in this respect than diminished hormone production at this time (the "deficient" luteal phase).

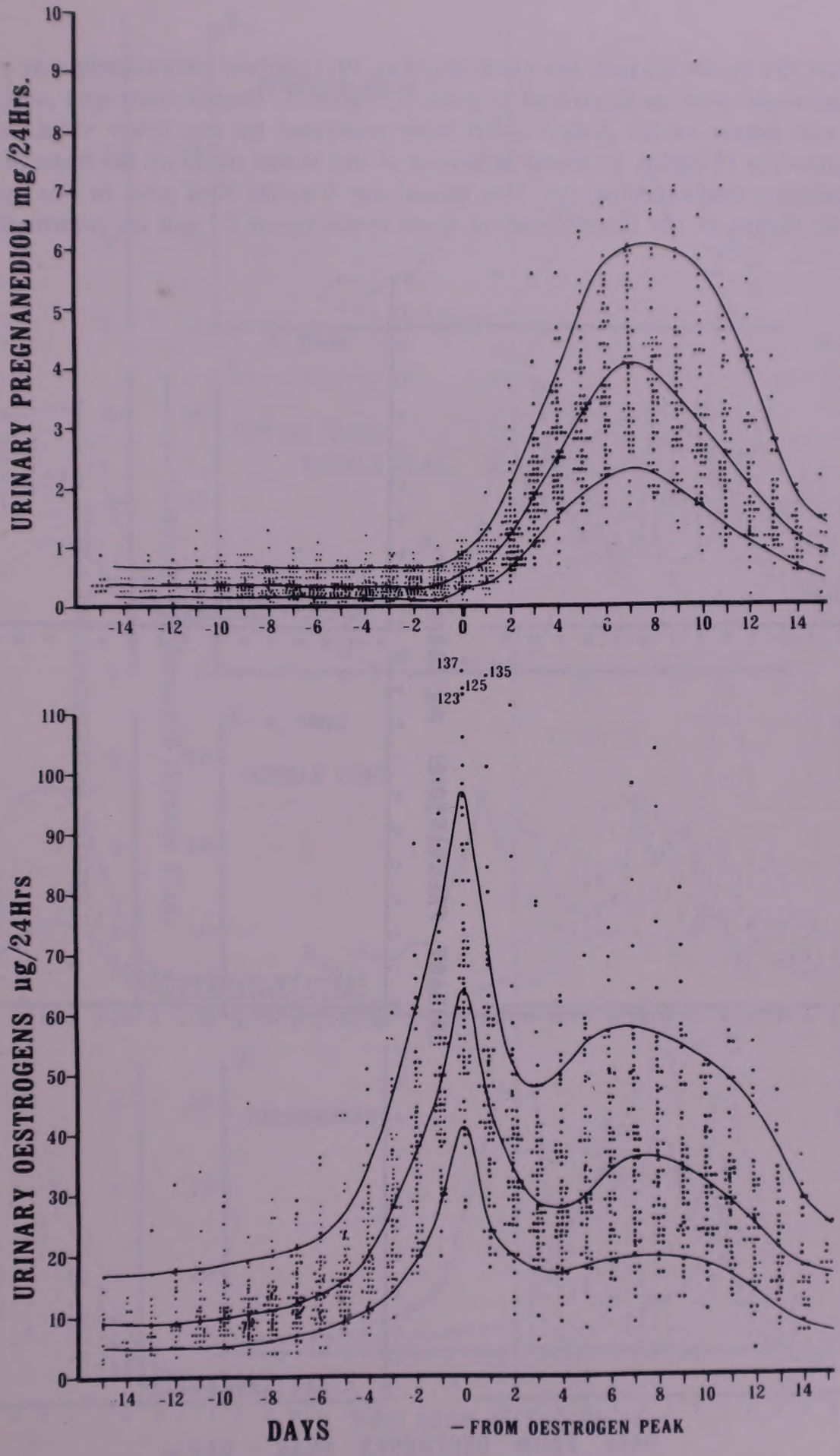

Figure 3. Daily urinary oestrogen and pregnanediol values in 61 ovulatory menstrual cycles from 26 parous and 14 nulliparous women aged 20–40 years. All values are plotted and the 10th, 50th and 90th percentile lines are shown. The mid-cycle oestrogen peak was defined for every cycle and days were numbered from this day (= day 0).

Of the 104 cycles studied, the great majority (91) showed an unambiguous mid-cycle oestrogen peak as illustrated in cycle A, Figure 5. Double oestrogen peaks in which two higher values 2 days apart were separated by one lower value, were encountered in 13 cycles. In these, definition of day 0 was made on the basis of the accompanying pregnanediol rise. This placed day 0 as the first peak in two cycles (cycle B, Figure 5), the second peak in seven cycles (cycle C) and the intermediate

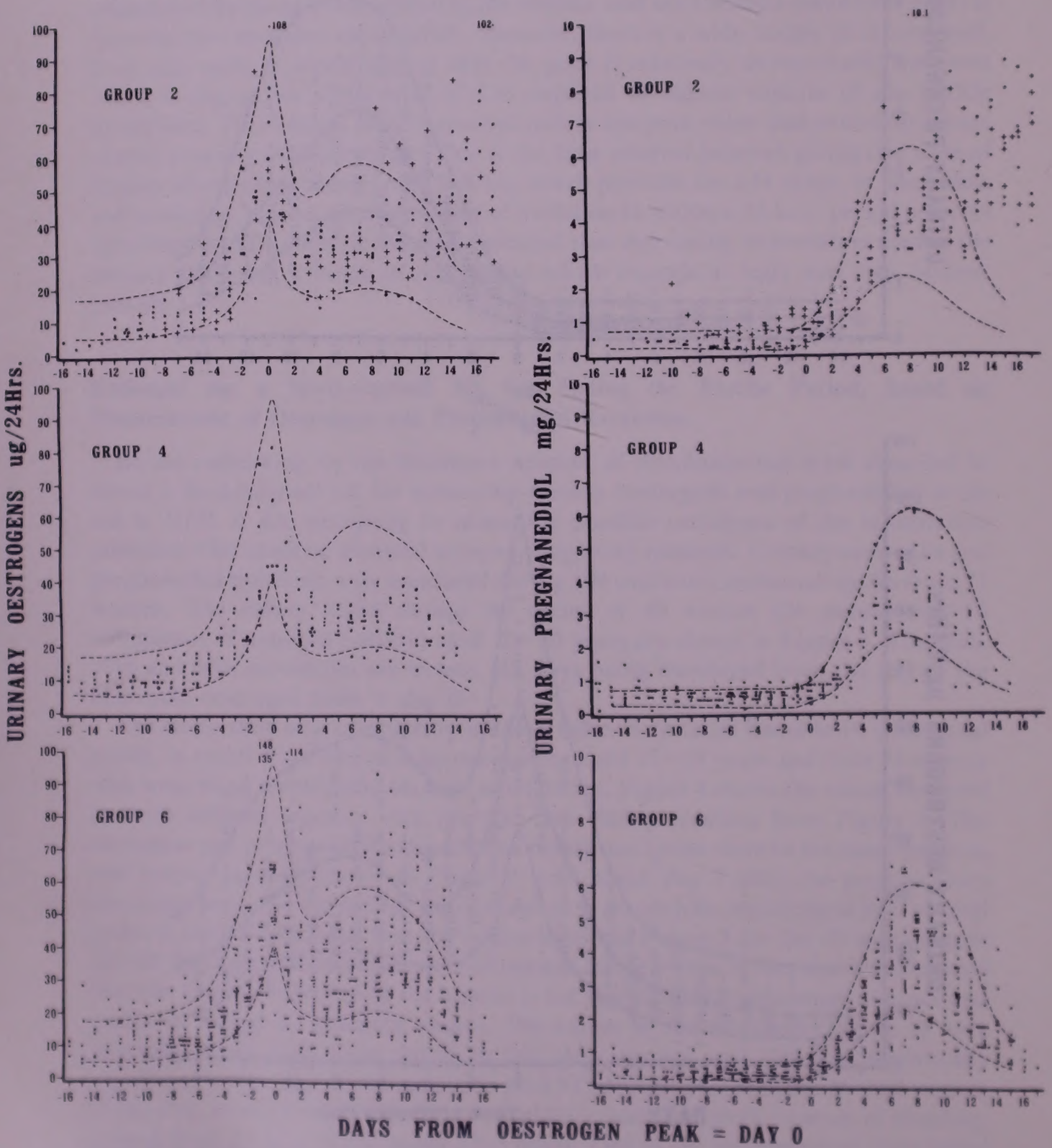

Figure 4. Daily urinary oestrogen and pregnanediol values during 10 conceptual cycles (group 2) and throughout the cycles of nine nulliparous women aged 17-19 years (group 4) and 24 "infertile" women (group 6). The dotted lines are the 10th and 90th percentiles from Figure 3.

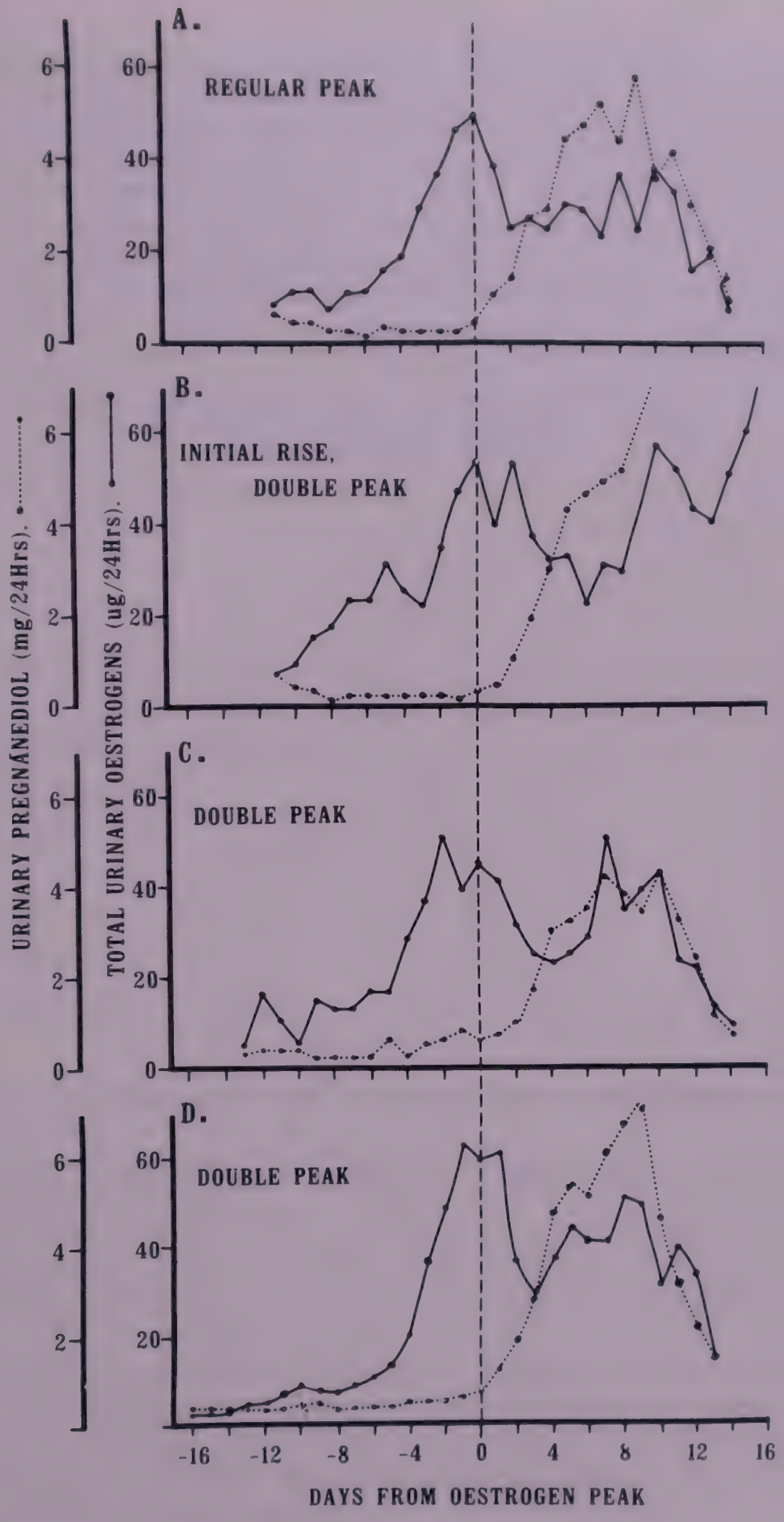

Figure 5. Types of pre-ovulatory oestrogen peaks encountered during the study of 104 ovulatory cycles. *A*, the usual regular peak; *B*, a conceptual cycle showing an initial non-ovulatory peak followed by a double pre-ovulatory peak; *C* and *D*, other types of double peaks. The vertical dotted line represents the best estimate of day 0 from the pregnanediol values.

value in four cycles (cycle D). Two of the conceptual cycles showed double peaks and therefore such a finding was not a bar to conception (cycle B, Figure 5).

Part of the information required from the study was whether identification of the first sustained oestrogen rise early in the cycle would provide sufficient warning of ovulation to be of value in NFP. A 6-day prediction would be ideal to allow for the longest sperm survivals. In all cycles in which sufficient information was obtained, there was a clear transition from early base-line oestrogen values, which in the majority (91%) fluctuated between 4 and 14 μg/24 hours, to the sustained rise which culminated in the pre-ovulatory oestrogen peak. In the remaining cycles, the base-line values fluctuated between 11 and 22 μg/24 hours. The interpretation of these trends is illustrated by the cycles shown in Figure 5; the first rise occurred on day -5 in cycle A, on day -4 in cycle C and on day -5 in cycle D. The day on which the oestrogen value first exceeded 15 μg/24 hours was also noted as this could be a useful point to set the sensitivity of a do-it-yourself kit. The day of the pre-ovulatory oestrogen peak has already been defined.

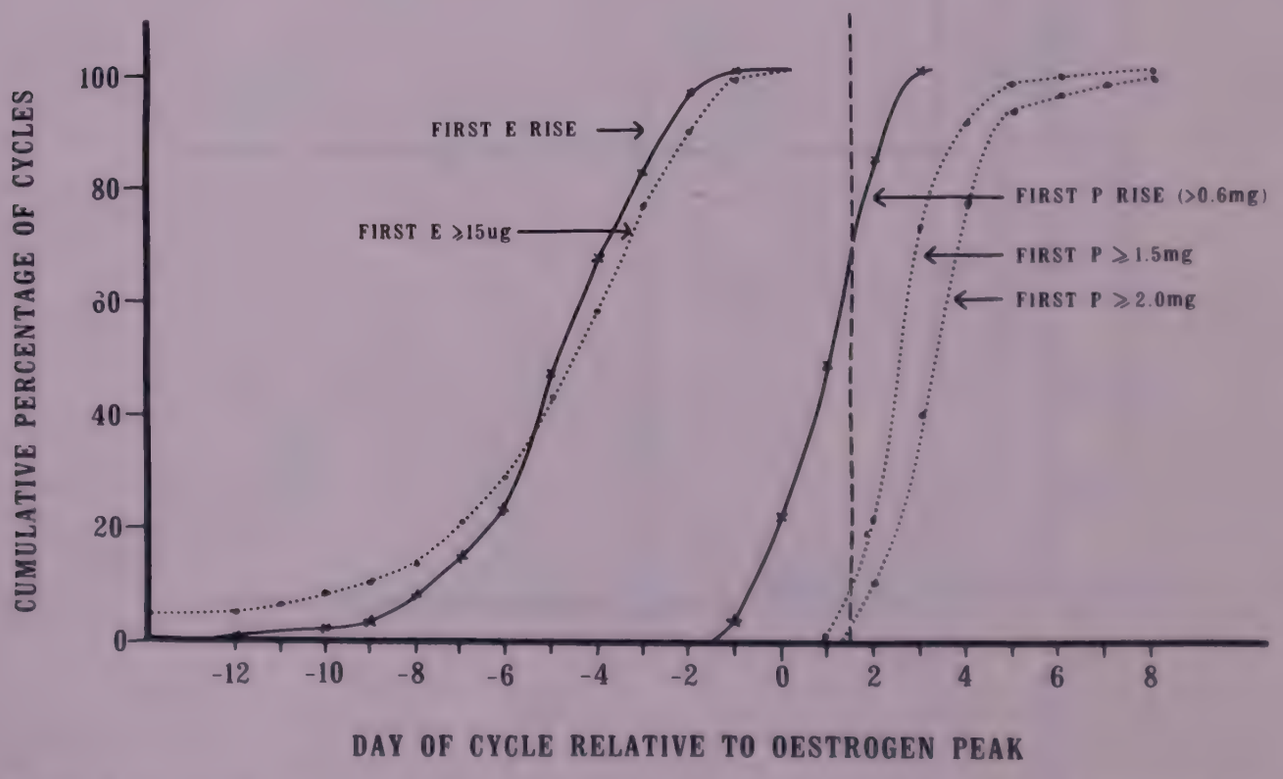

Figure 6. Cumulative percentage of cycles in which the events shown had occurred by a particular day. Days are numbered from the day of the pre-ovulatory oestrogen peak = day 0. The vertical dotted line indicates the best estimate of the moment of ovulation, which has a degree of uncertainty of approximately ± 12 hours. E = oestrogen, P = pregnanediol.

The pregnanediol values reached their lowest levels between days -7 and -1 (Figure 3). Thereafter, the values began to rise. The first pregnanediol rise was taken as the first day on which the values were clearly above the follicular phase base line and were exceeding 0·6 mg/24 hours. The first days on which the values exceeded 1·5 mg/24 hours and 2·0 mg/24 hours were also recorded, because 1·5 mg would be a convenient point at which to set the sensitivity of a do-it-yourself kit, and 2·0 mg is our level for concluding that ovulation has occurred. The combined results are summarized in Figure 6. The vertical dotted line shows the presumed time of ovulation, 37 hours after the oestrogen peak. Only 50% of the women would have

received a 6-day or more warning of ovulation from either the first oestrogen rise or the first value exceeding 15 μg/24 hours. The three women who had only 3 days warning were all trying to conceive and were having intercourse over this time. Although it is generally agreed that intercourse has no effect on inducing ovulation in the human, it is possible that ovulation, when it was imminent, could have been advanced by the acts of intercourse in these women. This phenomenon would operate to reduce the safety margins provided by the rules of the Ovulation Method, and is an important reason for avoiding any sexual activity during the fertile phase if pregnancy is to be avoided.

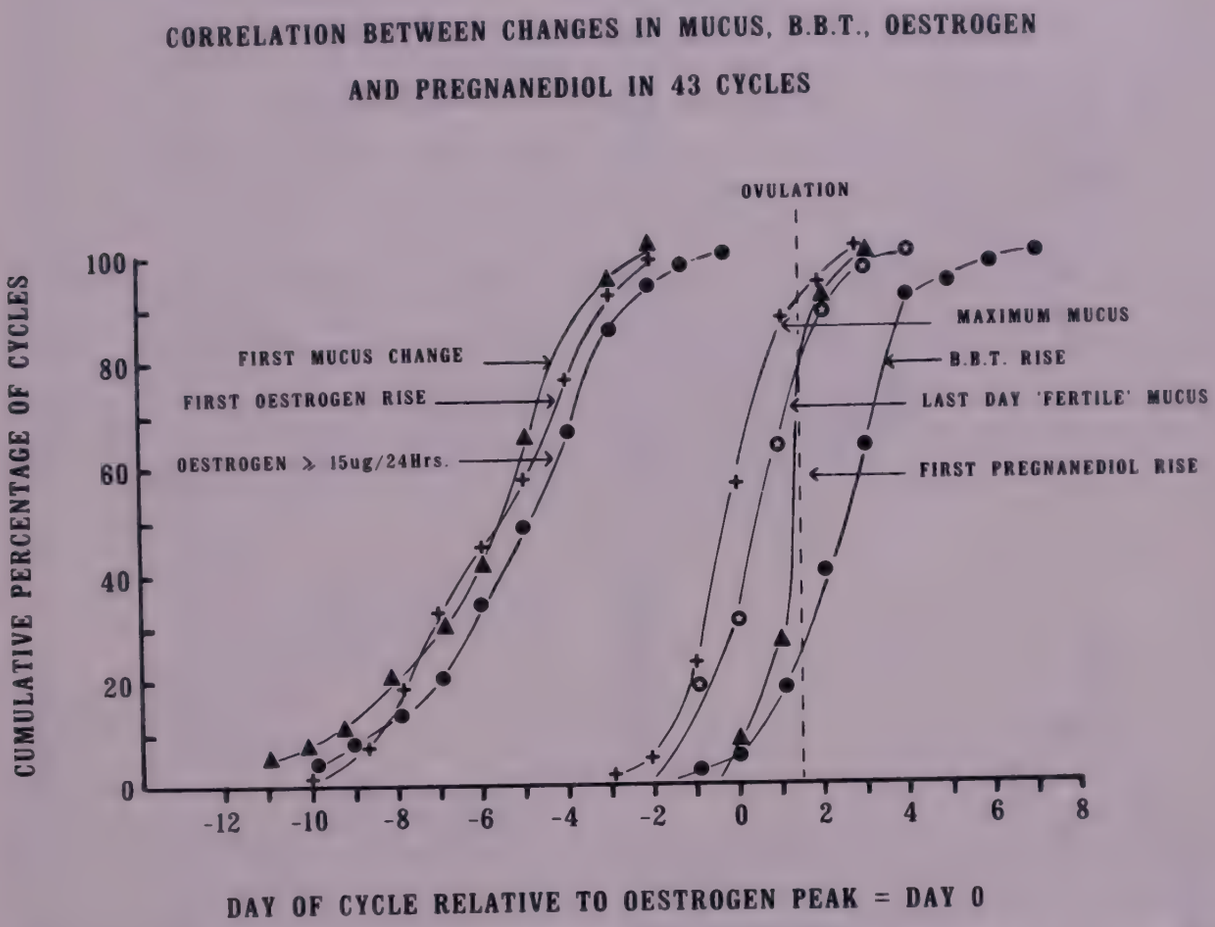

Figure 7. Cumulative percentage of cycles in which the events shown had occurred by a particular day. Days are numbered from the day of the pre-ovulatory oestrogen peak = day 0. The vertical dotted line indicates the best estimate of the moment of ovulation, which has a degree of uncertainty of approximately ± 12 hours.

It could be argued from these findings that a do-it-yourself kit based on oestrogen estimation would not provide sufficient warning of ovulation in a high enough percentage of women to be of value in defining the beginning of the fertile phase for NFP. However, it is likely that oestrogens are involved in providing the necessary support for the sperm in the female genital tract and that the women with the shortest warning are also those with the shortest sperm survivals. This can be tested only by applying these assays to a large population of women applying NFP, a project which would be most difficult at the present time.

There is little problem in the application of a do-it-yourself kit for pregnanediol estimation. In approximately 10% of cycles a value of 1·5 mg/24 hours was reached as early as the second day after the oestrogen peak, that is within 12 hours after the

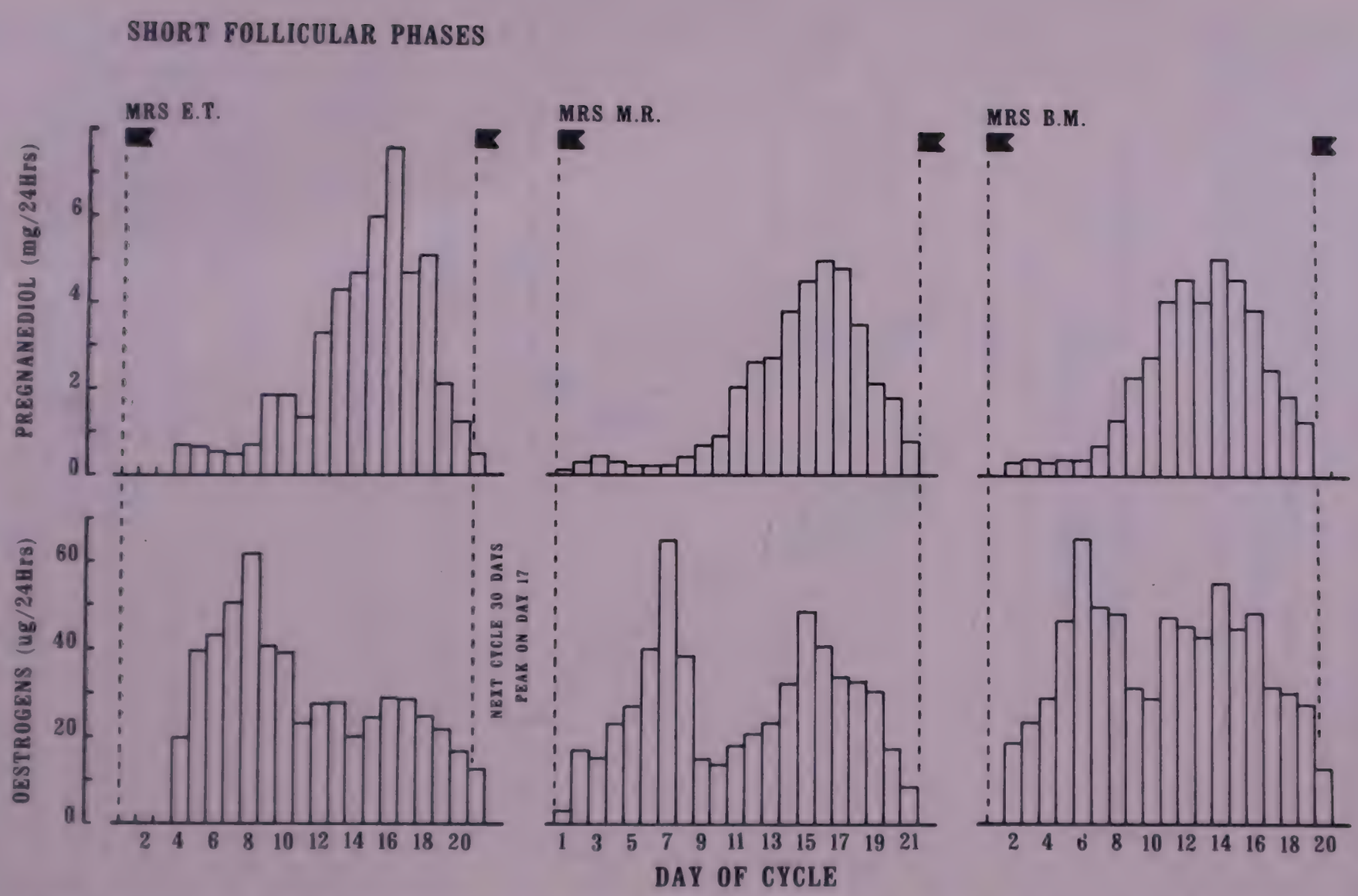

Figure 8. Daily urinary oestrogen and pregnanediol values during three short ovulatory cycles of 19–21 days duration. The pre-ovulatory oestrogen peaks occurred on days 6–8 of the cycles.

presumed time of ovulation. This might not be considered an adequate safety margin, but it is likely that this early rise in progesterone would alter the cervical mucus so that late transit of sperm was prevented. If this did not prove to be a fail-safe mechanism, rules could be formulated to postpone intercourse for a specified number of days until complete safety was assured.

Recently another series of 43 ovulatory cycles has been completed in which the women recorded the first change from the basic infertile pattern (as formulated by the rules of the Ovulation Method), the day of maximum mucus production, the last day of fertile mucus and the BBT. Daily urine specimens were collected throughout the cycle and the first oestrogen rise and the pre-ovulatory oestrogen peak, together with the luteal phase rise in pregnanediol were recorded. The cumulative distribution of the results is shown in Figure 7. The first mucus change coincided almost exactly with the first oestrogen rise, the correlation coefficient relating the two events being 0·89. This is about as perfect agreement as could be expected from the observation of two physiological phenomena. The cumulative distribution patterns for the mid-cycle events were almost identical with those found in the earlier studies (Figures 2 and 6), thus confirming the validity of those observations. The correlation coefficient relating the day of the pre-ovulatory oestrogen peak with the day of the maximum mucus production was 0·95 and the coefficient relating the oestrogen peak with the last day of fertile mucus was also 0·95. (A perfect agreement would give a correlation coefficient of 1·0.) Thus there is no doubt that the self-observed mucus symptoms are a very accurate reflection of the underlying ovarian activity.

Unusual Cycles

Some unusual patterns were recorded during the study. Figure 8 shows three unusually short cycles of 20–21 days duration. At one time it was thought that very short cycles of 3 weeks or less were anovulatory. However, these three cycles had all the hormone characteristics of the fertile cycle, apart from unusually short follicular phases. It is because such cycles may be encountered with ovulation occurring on days 7–9 after onset of bleeding, or 2–5 days after cessation of bleeding, that days of the menstrual flow are not considered to be safe. Other unusual patterns are illustrated in Figure 9, in which the eight markers were recorded in three subjects. A long cycle of 45 days duration was encountered in one subject (Mrs. S) with a follicular phase of 30 days. This woman recorded patches of fertile-type mucus (grading greater than 4) as the oestrogen values rose above 10 μg/24 hours. A value of 10 μg/24 hours or more represents the urinary level at which secretion of the potent oestrogen, oestradiol, by the ovarian follicles becomes significant and is sufficient to cause production of fertile-type mucus and also stimulation of the endometrium. Levels below 10 μg/24 hours are contributed by extraglandular conversion of androgens to oestrogens which have little biological activity. It is unusual to find continuing production of fertile mucus over long periods of time, even when the oestrogen values are persistently elevated. It would seem that when the oestrogen values are elevated, but relatively constant, cervical mucus is produced in bursts lasting for several days rather than as a continuous secretion.

Figure 9 shows a cycle (Mrs. C) in which ovulation was about to occur, but it was suppressed by a severe infection and then took place 7 days later. This finding illustrates that any stress, such as illness, severe emotional upset, or surgery can affect the ovulatory rhythm, and this must be anticipated when applying NFP. The rules of the Ovulation Method coped with these unusual events in this cycle. It should be noted that the beginning of the luteal phase rise in progesterone starting on day 21 and

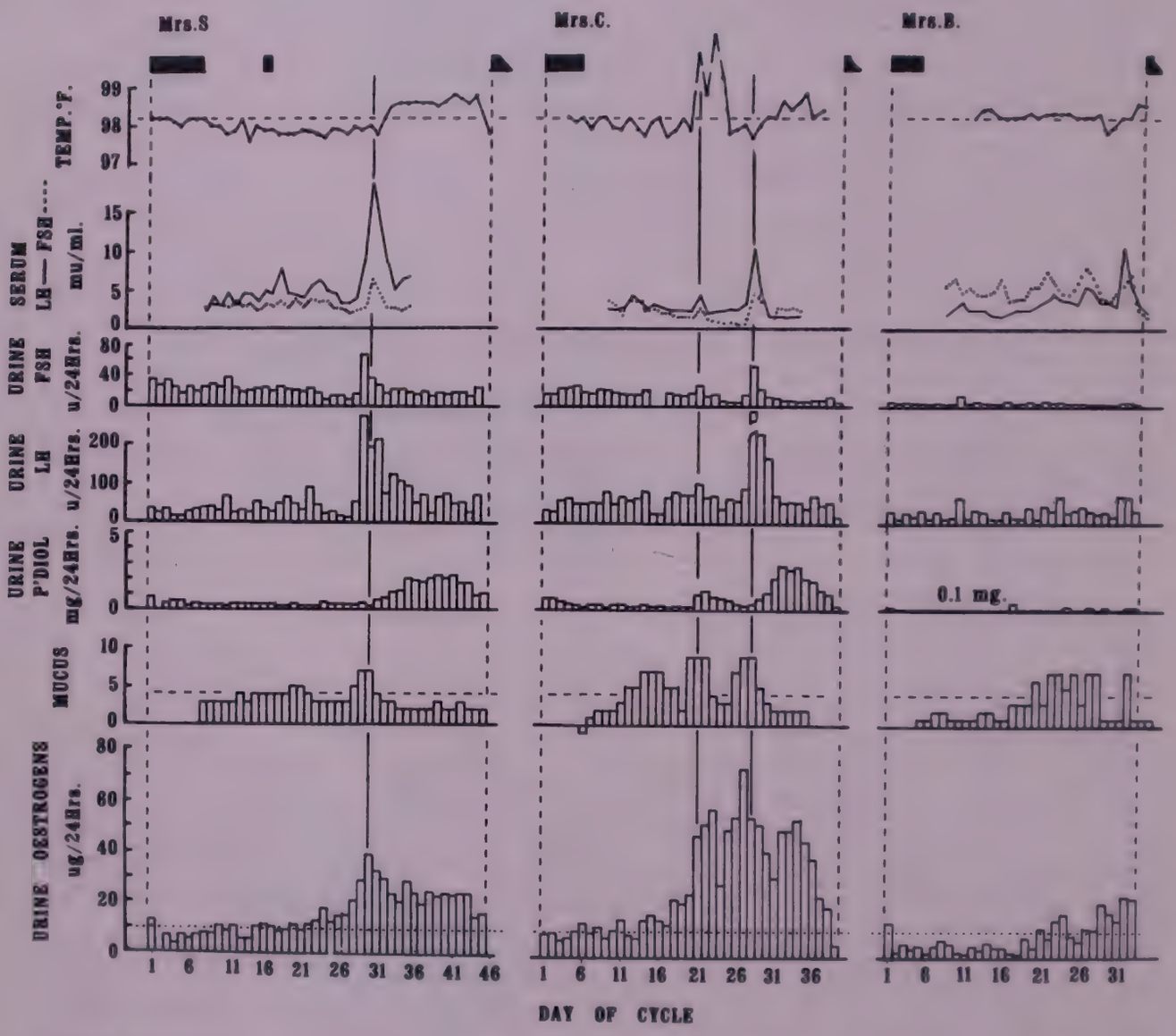

Figure 9. Daily urinary oestrogen and pregnanediol values, mucus scores, urine LH and FSH, serum LH and FSH and BBT in three unusual cycles, one with a prolonged follicular phase (Mrs. S), one with double mid-cycle markers due to a severe infection (Mrs. C) and an anovulatory cycle (Mrs. B). The vertical solid lines are the days of the serum LH peaks, the dotted vertical lines are the first days of bleeding, the horizontal dotted lines mark the 10 μg/24 hour level of urinary oestrogens (commencing ovarian activity), the transition from infertile to fertile-type mucus, and the marginal line for BBT.

subsiding 3 days later, overruled the effect on the cervical mucus of the continuing high oestrogen values at this time and reduced the score to below 4. It is the rise in progesterone which causes the abrupt change from fertile to infertile mucus, which defines the "peak" day at ovulation, rather than the accompanying fall in oestrogen values. In this subject, the first patches of fertile mucus were recorded as the oestrogen values rose above 10 μg/24 hours (days 11 and 14–16 of the cycle).

Mrs. B (Figure 9) had an anovulatory cycle during the period of study, as shown by the persistently low pregnanediol values. The oestrogen values rose gradually during the last half of the cycle and bleeding occurred as a breakthrough phenomenon. Again patches of fertile mucus were observed as the oestrogen values rose above 10 μg/24 hours. Irregular patches of mucus throughout a cycle or mucus appearing shortly before menstrual bleeding are indications that the cycle is anovulatory (Figure 10).

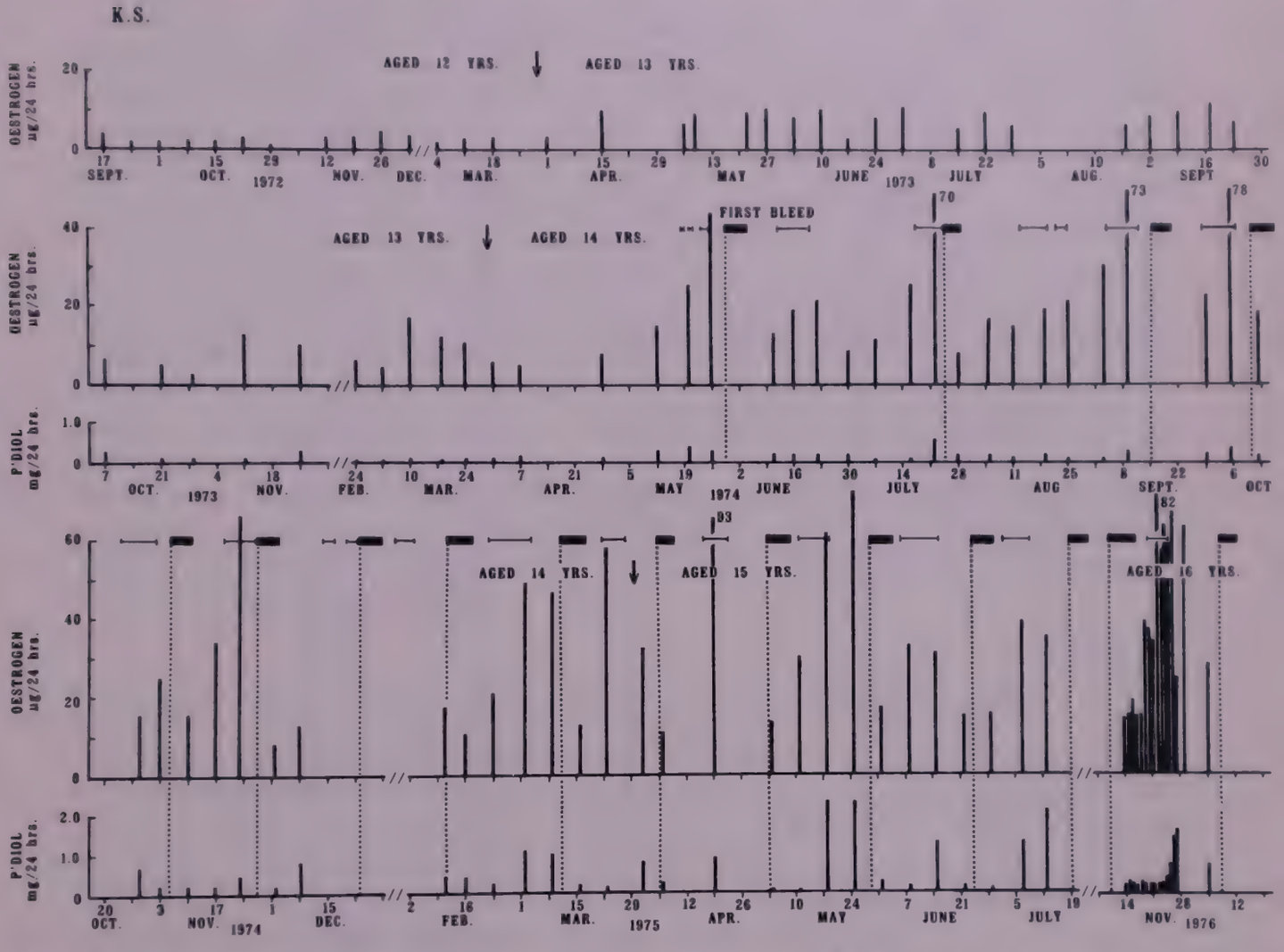

Figure 10. Weekly urinary oestrogen and pregnanediol values measured over a 5-year period in a girl aged between 11 and 16 years. Menarche occurred on May 28, 1974, at the age of 14 years and first ovulation occurred on approximately May 14, 1976, at the age of 15 years. Dotted vertical lines are the first days of bleeding; —— = patches of fertile-type mucus. Arrows are birthdays.

Hormone Values and Mucus Patterns in Girls from Childhood to First Ovulation

Seven girls have been studied for periods of up to 5 years as they passed from childhood to adulthood (Brown *et al.* 1978). The most complete study which illustrates the results obtained is shown in Figure 10. The urinary oestrogen and pregnanediol values are shown together with the observations of bleeding and of fertile-type mucus (designated by the horizontal bars between episodes of bleeding). At age 12½ years the oestrogen values were fluctuating rhythmically between 1·2 and 2·6 μg/24 hours. The fluctuations increased in amplitude during the age of 13 years, the highest values recorded being 17 μg/24 hours in March, 1974. In May,

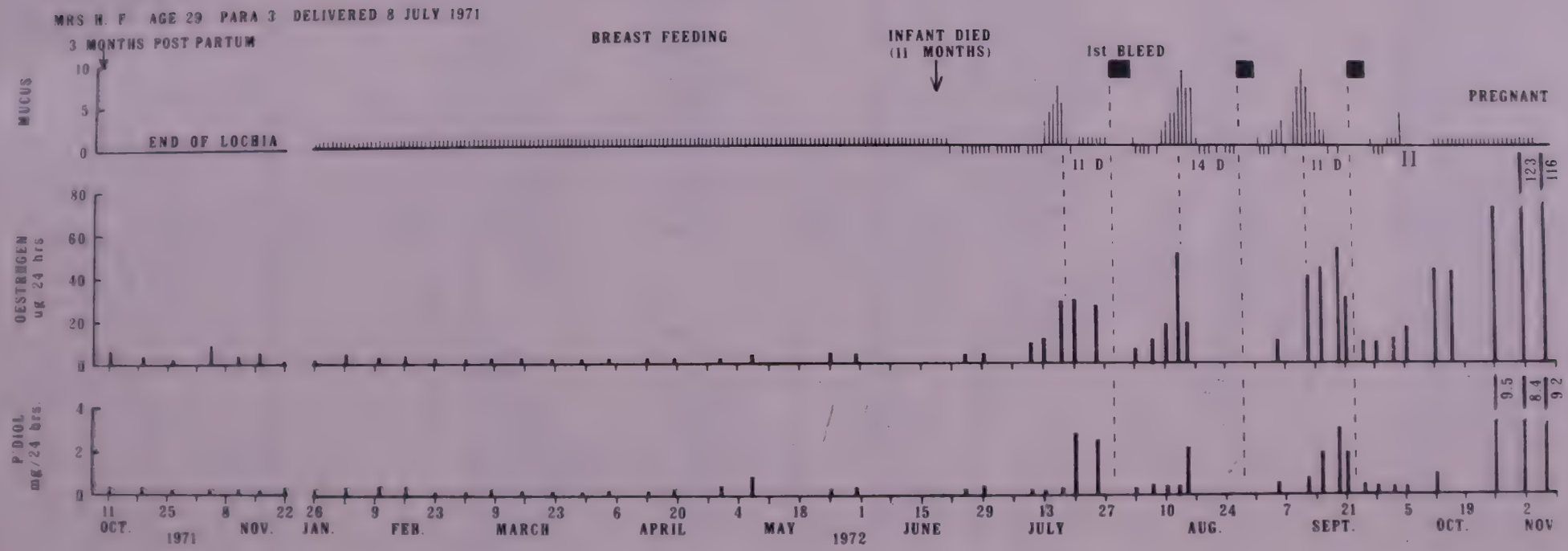

Figure 11. Weekly urinary oestrogen and pregnanediol values and daily mucus scores during lactation amenorrhoea, first ovulation and pregnancy. In this and subsequent figures, the dotted vertical lines represent the first days of bleeding and the best estimates of the days of ovulation. The calculated lengths of the luteal phases are shown. I = intercourse.

she noticed that mucus production was increasing and changing in quality and at this time the oestrogen values peaked to 44 μg/24 hours. She experienced her first bleed (menarche) 2 days later. The subsequent pattern showed fluctuating oestrogen values peaking to 70 μg/24 hours and patches of fertile-type mucus immediately preceding the episodes of bleeding. The periodicity of the bleeding phases was 8 weeks at first, but this finally settled to a monthly rhythm.

During the ages of 12 and 13 years, the pregnanediol values remained uniformly low, being less than 0·3 mg/24 hours. However, a value of 0·4 mg/24 hours was recorded 9 days before the first bleed in May, and a value of 0·6 mg/24 hours was recorded before the second bleed in July. The premenstrual rises in pregnanediol increased in amplitude and before the 9th bleed in March, 1975, first exceeded 1 mg/24 hours for two consecutive weeks. In May, 1975, the pregnanediol values first exceeded 2 mg/24 hours for two consecutive weeks, the criterion for ovulation. During this sequence the patches of fertile-type mucus ceased for longer and longer intervals before menstruation, reflecting the inhibitory effects of the progesterone being produced during the latter parts of the cycles. Regular ovulatory cycles with luteal phases of approximately 14 days, became established as was demonstrated by the cycle studied at age 16 years. It can thus be concluded that cyclical ovarian activity was occurring during the 1−2 years before menarche, that the fluctuations in oestrogen excretion increased until menarche occurred, that the initial menstrual cycles were anovulatory of the fluctuating oestrogen type and these changed gradually to become fully ovulatory cycles a year after menarche. Figure 10 illustrates mucus patterns in anovulatory cycles and the processes by which the ovulatory mechanism matures at the ovarian level.

Hormone Values and Mucus Patterns Postpartum and during Lactation

The months after childbirth constitute a difficult time for the application of most methods of NFP. We have studied 42 women for periods of up to a year or more by serial or weekly oestrogen and pregnanediol assays. The results from four women will be shown to illustrate the enormous amount of data which has been obtained from this study. The daily mucus scores are shown as fine vertical lines and the weekly oestrogen and pregnanediol values by the heavier lines.

Figure 11 shows the results obtained in a woman (Mrs. H.F.) who breast-fed her infant until it died of encephalitis at the age of 11 months. The study commenced at 3 months postpartum, and throughout the next 8 months, the oestrogen and pregnanediol values remained uniformly low, generally being less than 5 μg/24 hours and 0·4 mg/24 hours respectively, values characteristic of absent ovarian activity. After cessation of lochia, the subject recorded minimal unchanging mucus production, with a score of +1. This represented her basic infertile pattern and because it was unchanging it indicated unchanging ovarian activity which is, of course, incompatible with cyclic activity, ovulation and fertility. The mother expressed her milk while the infant was in intensive care, but after it died and lactation ceased, ovarian activity resumed within 3 weeks and ovulation within 4 weeks, followed by a luteal phase of 11 days. Two ovulatory cycles with luteal phases of 14 and 11 days followed. In the next cycle pregnancy was attempted and achieved by concentrating intercourse (I on the chart) on the time of maximum fertile mucus production.

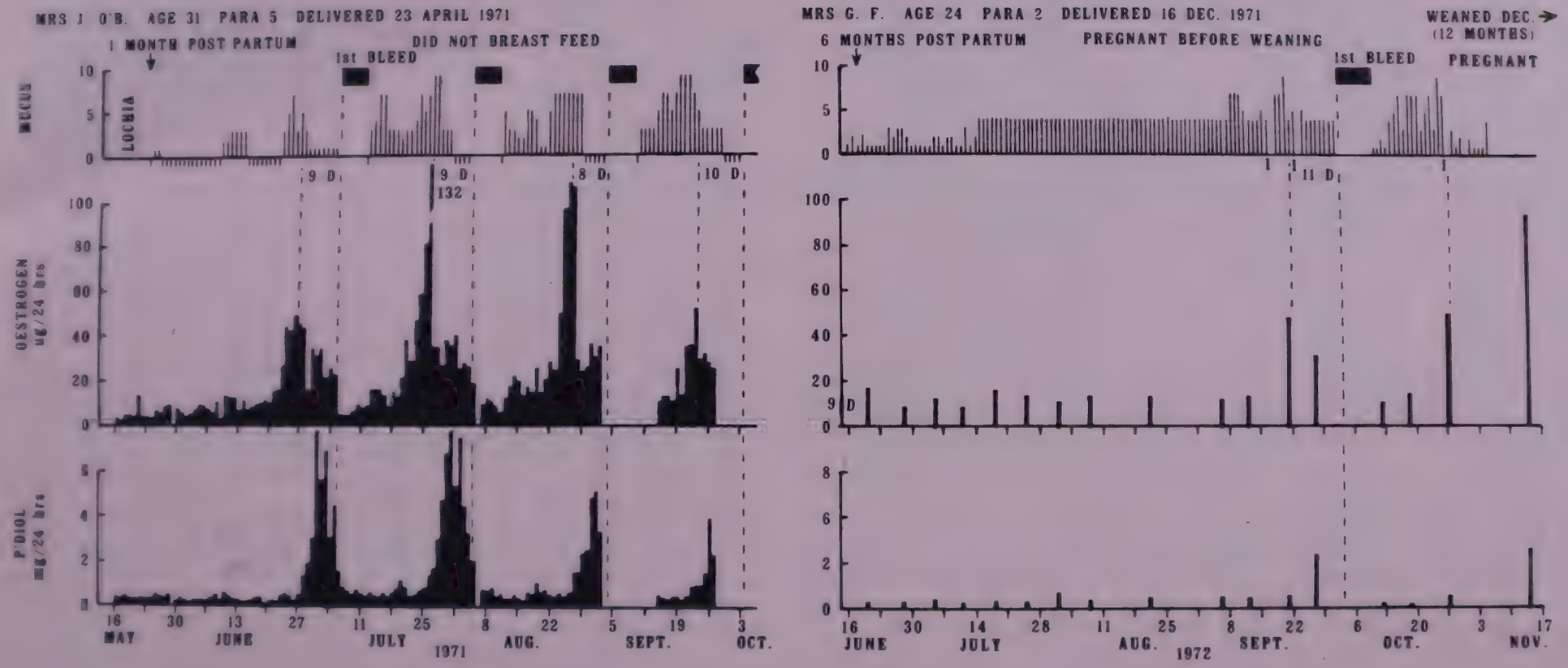

Figure 12. Urinary oestrogen and pregnanediol values and daily mucus scores postpartum in a subject who did not breast-feed (Mrs. J.O'B) and another subject who conceived during breast-feeding (Mrs. G.F.).

Figure 12 shows the results obtained in two subjects. Mrs. J.O'B. did not breast-feed her infant. The oestrogen values postpartum were initially very low (4 μg/24 hours) but by 7 weeks they had exceeded 10 μg/24 hours and ovulation occurred at 9 weeks. This was followed by a short luteal phase of 9 days. Regular ovulatory cycles with short luteal phases of less than 11 days were still occurring 5 months after delivery. The overall study of the 42 women showed that short luteal phases, which would not have been fertile, were common in ovulatory cycles which occurred before 6 months postpartum. These were presumably due to the raised prolactin values at this time. This subject illustrates the rapid return to ovulatory ovarian activity in women who do not breast-feed.

Mrs. G.F. (Figure 12) was not family-planning. She conceived while breast-feeding during her second cycle, which occurred 10 months postpartum. Her basic infertile mucus pattern had the unusually high score of 4, which was associated with high basal oestrogen values (10–20 μg/24 hours).

Figure 13 demonstrates returning fertility in a woman who breast-fed her infant for the unusually long period of 30 months. Amenorrhoea persisted for the first 17 months. The study commenced at 13½ months postpartum, at which time the oestrogen values were already fluctuating between 2 and 15 μg/24 hours. Patches of fertile-type mucus were recorded corresponding approximately to the elevations of the oestrogen values above 10 μg/24 hours. In January, 1972, the subject observed mucus symptoms which were unmistakably like those she had experienced at ovulation before pregnancy. She started collecting urine specimens and the latter part of an ovulatory cycle was recorded, which, on the basis of the mucus symptoms, had a luteal phase of 12 days duration. Specimens were collected for another 5 months with continued breast-feeding, and during this time five ovulatory cycles were recorded, all with normal lengths of luteal phases (13–15 days) and therefore presumably fertile.

The results obtained in the 42 women confirmed many of the current views on returning fertility postpartum. They demonstrated that (1) the return of ovarian activity is a very variable event; (2) in the absence of breast-feeding, ovulatory ovarian activity returns rapidly, in the example shown within 2 months, but short luteal phases (infertile) were common in these initial cycles; (3) during lactation amenorrhoea, the ovaries may be completely inactive or may show minimal cyclic activity which gradually increases until bleeding results; (4) the initial ovarian activity may be ovulatory or anovulatory, and the luteal phases of the initial ovulatory cycles may be shorter than normal, particularly when they occur within the first 9 months postpartum; (5) return of fertility is accelerated by weaning; (6) when return of fertility has been delayed for long periods of time by continued breast-feeding, the first cycle is likely to have all the characteristics of the normal, fertile, ovulatory cycle; and (7) in this group of women, the finding of fertile-type mucus gave many false positive indications of fertility, which restricted intercourse, but no false negatives; this was expected because fertile-type mucus is a result of any ovarian activity, whereas the "peak" mucus symptom is the result of ovulation (fertility).

The study of postpartum women allowed a detailed correlation to be made between urinary oestrogen values and the corresponding mucus scores in the absence of inhibition by progesterone. This correlation is shown for 778 observations in Figure 14, which includes observations made by women who were learning the Ovulation Method for the first time. When the mucus score was less than 3, the urinary oestrogen values were generally less than 10 μg/24 hours (absent ovarian activity).

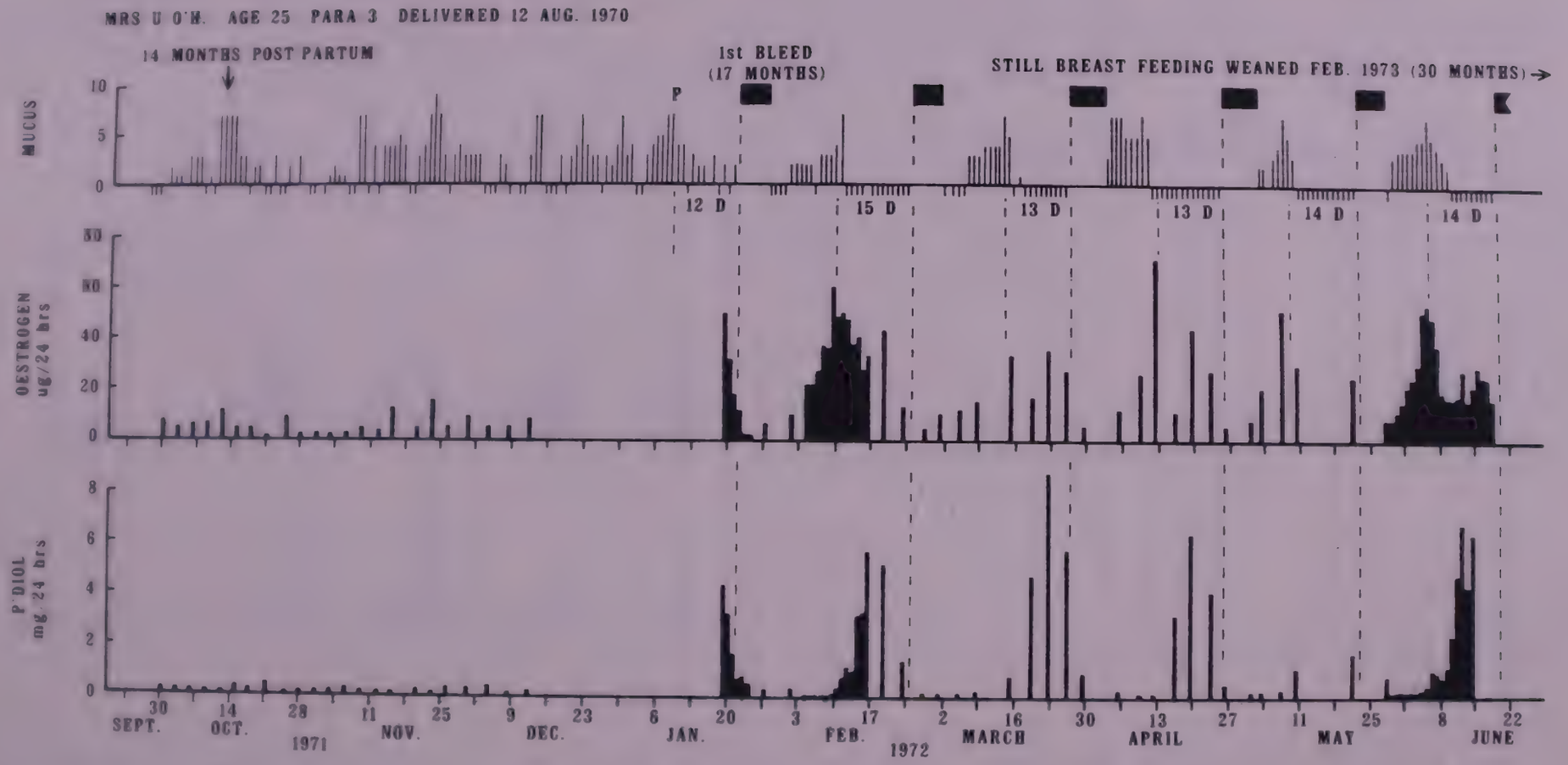

Figure 13. Urinary oestrogen and pregnanediol values and daily mucus scores in a subject who breast-fed for 30 months. First ovulation postpartum occurred 17 months after delivery.

When highly fertile mucus was recorded (scores 7 and 9) the urinary oestrogen values were generally above 15 μg/24 hours. The overall correlation coefficient for this association was 0·71. Some obvious discrepancies occurred in which high oestrogen values were associated with low scores and low oestrogen values with high scores. However, such discrepancies were relatively uncommon (23 out of 778 observations or 3%) and have several explanations including the episodic nature of mucus production, time delays between oestrogen and progesterone production and excretion and mucus responses, and errors in mucus observations due to inexperience, unrecorded acts of intercourse and other factors.

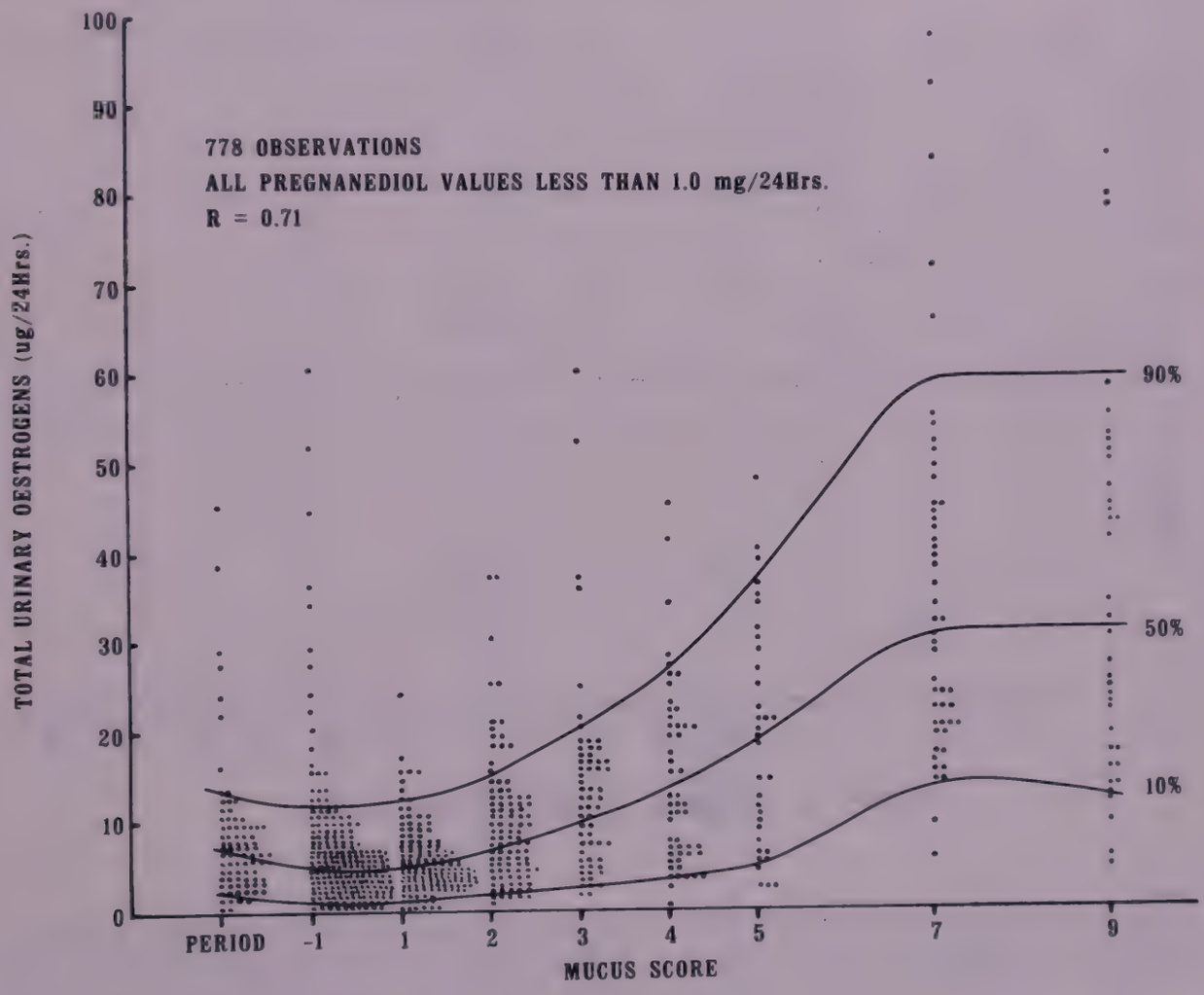

Figure 14. Correlation between 778 urinary oestrogen values and cervical mucus scores recorded during the same 24-hour periods in 42 postpartum women. All associated urinary pregnanediol values were low (less than 1·0 mg/24 hours). The 10th, 50th and 90th percentiles are shown. Period = days of bleeding.

Other information required from the data was whether the mucus symptoms provided sufficient warning of returning fertility (ovulation) to be of value in NFP. This information was available for 37 of the women. The numbers of days between the point of change from the basic infertile mucus pattern to the estimated date of ovulation in the first cycle postpartum are showed in Figure 15. Twenty-three women had 6 days or more warning, whereas 14 had less warning. However, of these 14 women, 11 had short luteal phases of 10 days or less and would, therefore, not have been fertile in that cycle because of insufficient time for implantation (regression of

the corpus luteum begins 3–5 days before bleeding). The remaining three had adequate luteal phases with ovulatory levels of pregnanediol (Figure 15); two of these had warnings of 3 days and the other of 4 days. These would have represented failures of the method if they had conceived. However, inspection of the cycles of the few subjects who did conceive by mistake, showed a series of near misses in previous cycles which ought to have warned them to be more vigilant.

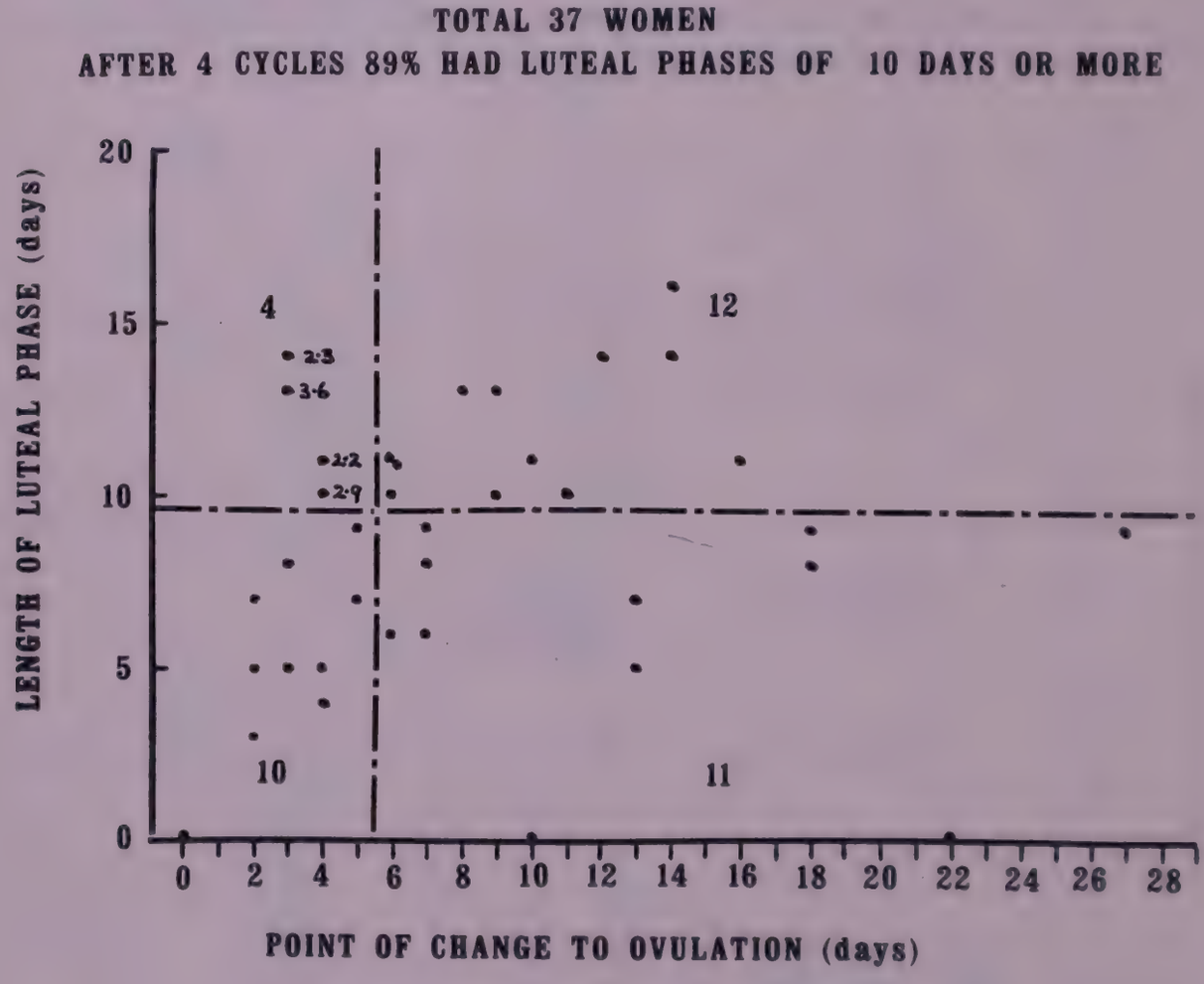

Figure 15. Days between the first point of change in the mucus pattern to the best estimate of ovulation during the first postpartum ovulatory cycles of 37 women. The subjects are divided into four groups according to whether a warning of 6 days or more was provided and whether the luteal phase was of adequate length (11 days or more). The numbers in the upper left-hand quadrant refer to the pregnanediol values reached during the luteal phase.

Hormone Values and Mucus Patterns during the Climacteric Years Preceding the Menopause

Hormone studies have been performed in 85 climacteric women, the criterion for inclusion being the onset of irregular cycles after a life-time of regularity. Two of these subjects were studied by weekly collections for periods of time covering 6–7 years (Figures 16 and 17). In these two figures, the urinary oestrogen and pregnanediol values, the mucus scores and the times of bleeding and spotting are plotted as for the postpartum women. The estimated times of ovulation are shown as vertical lines, immediately below the mucus scores.

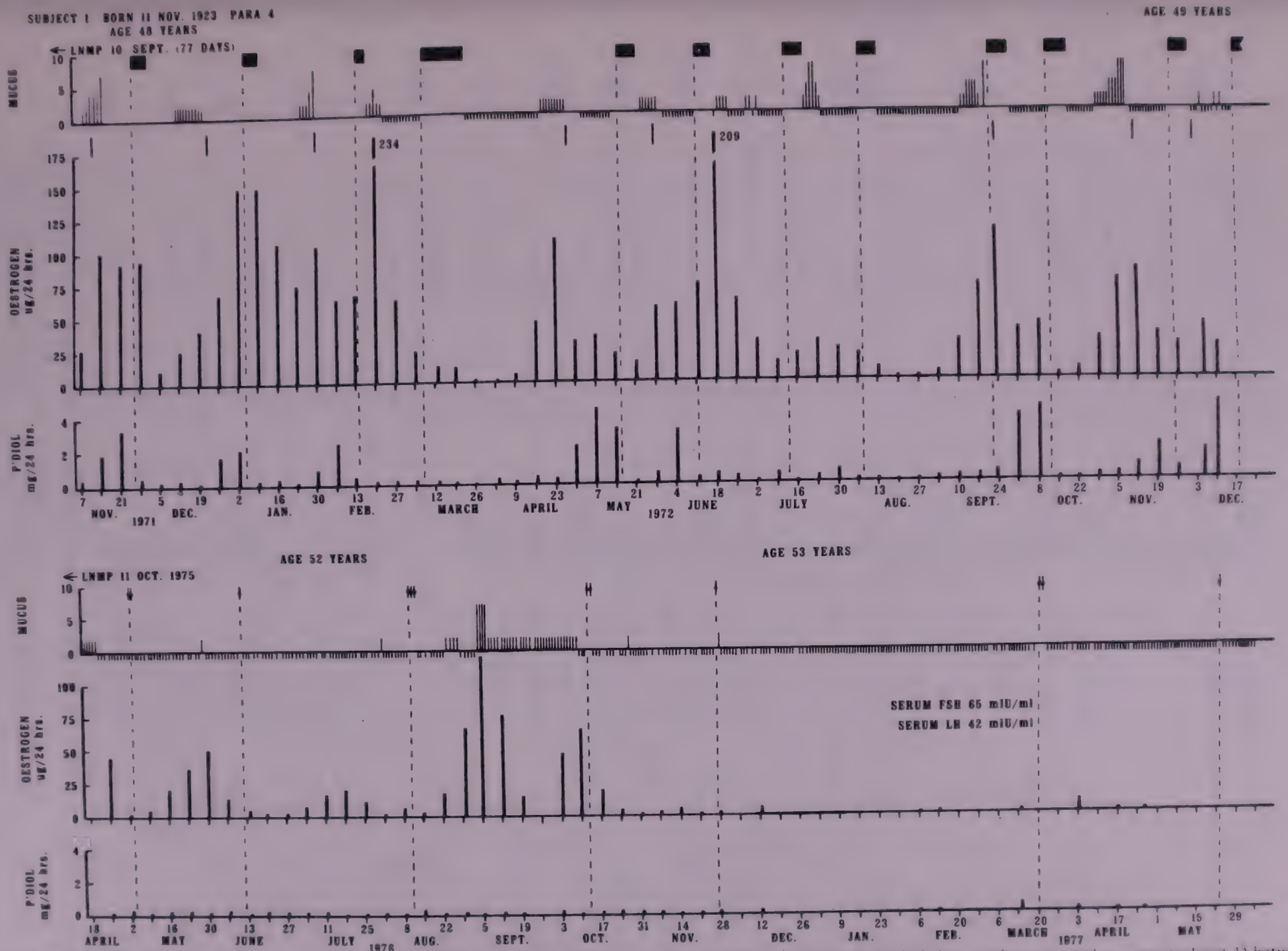

Figure 16. Weekly urinary oestrogen and pregnanediol values and daily mucus scores over two 13-month periods in a perimenopausal woman (subject 1) between the ages of 48 and 53 years. The short vertical lines under the mucus scores are the best estimates of the times of ovulation. ⫴ = spotting.

Subject 1 (Figure 16) was aged 48 years at the beginning of the study and had just recorded an unusual period of amenorrhoea which had lasted for 58 days. The results demonstrated that this prolonged cycle was ovulatory, with a luteal phase of 14 days duration. The next cycle in December lasted 40 days and was also ovulatory according to the pregnanediol values, but the oestrogen values remained elevated (150 μg/24 hours) during the bleeding phase. This is an uncommon pattern and is presumably due to the development of new follicles or a follicular cyst during the luteal phase. The next cycle showed a similar pattern of luteal phase levels of pregnanediol excretion and rising oestrogen values at the time of bleeding. The February cycle, which lasted 23 days, was anovulatory with peak oestrogen values reaching the very high value of 234 μg/24 hours. The April cycle was ovulatory with a long follicular phase and lasted 69 days. The next cycle again showed the abnormal ovulatory pattern of the December and January cycles, with high rising oestrogen values at the time of bleeding. The following two cycles in July were anovulatory, one with high peak oestrogen values of 209 μg/24 hours, the other being of the constant oestrogen type. The next complete cycle lasted 64 days; it was ovulatory with a prolonged follicular phase and a breakthrough pre-ovulatory bleed occurring on the 22nd September. Both the November and December cycles were ovulatory. Thus, in one year this subject had demonstrated practically every pattern of normal and abnormal ovarian activity yet demonstrated. Although changes to fertile-type mucus were documented near ovulation in all the ovulatory cycles except the last, some of the changes were less than is usually expected at this time. It should be noted that the very high oestrogen values which occurred in the anovulatory cycles during February and June were not associated with highly fertile-type mucus, even though the corresponding pregnanediol values were low. This is a frequent finding in such anovulatory cycles in older subjects and the explanation is not known. This couple used the frequent "dry" days for intercourse. The only time that this rule might have failed was in the December, 1972, cycle, when the mucus pattern did not show that ovulation was occurring. The absence of fertile-type mucus during this cycle is explained by the higher than normal pregnanediol values early in the cycle which would have been a bar to mucus production and fertility.

This subject continued to have irregular cycles during the next 4 years, during which she was never well and suffered from many climacteric complaints. Several checks were performed to exclude malignancy. Collections were recommenced in April, 1976, at the age of 52 years following amenorrhoea for 6 months. Anovulatory ovarian activity was still occurring, with periodicities of 1–2 months. The peak oestrogen values reached 50 μg/24 hours in April and May and 125 μg/24 hours in September. In spite of these considerable fluctuations, menstrual bleeding did not ensue and only slight spotting was observed. Furthermore, apart from the September peak, the mucus symptoms failed to show the responses to these oestrogen values expected from the studies performed in younger women. It was as if the endometrium and cervix were losing the receptors required to respond to the ovarian oestrogen being introduced. The pregnanediol values remained at uniformly low levels throughout this year and the subject was obviously infertile during this time. After the October activity, the oestrogen values remained at the very low levels characteristic of post-menopausal women. In February, measurements of serum FSH and LH showed that these were in the post-menopausal range. The study was terminated in April, although episodes of slight spotting without change in the oestrogen values were still being observed.

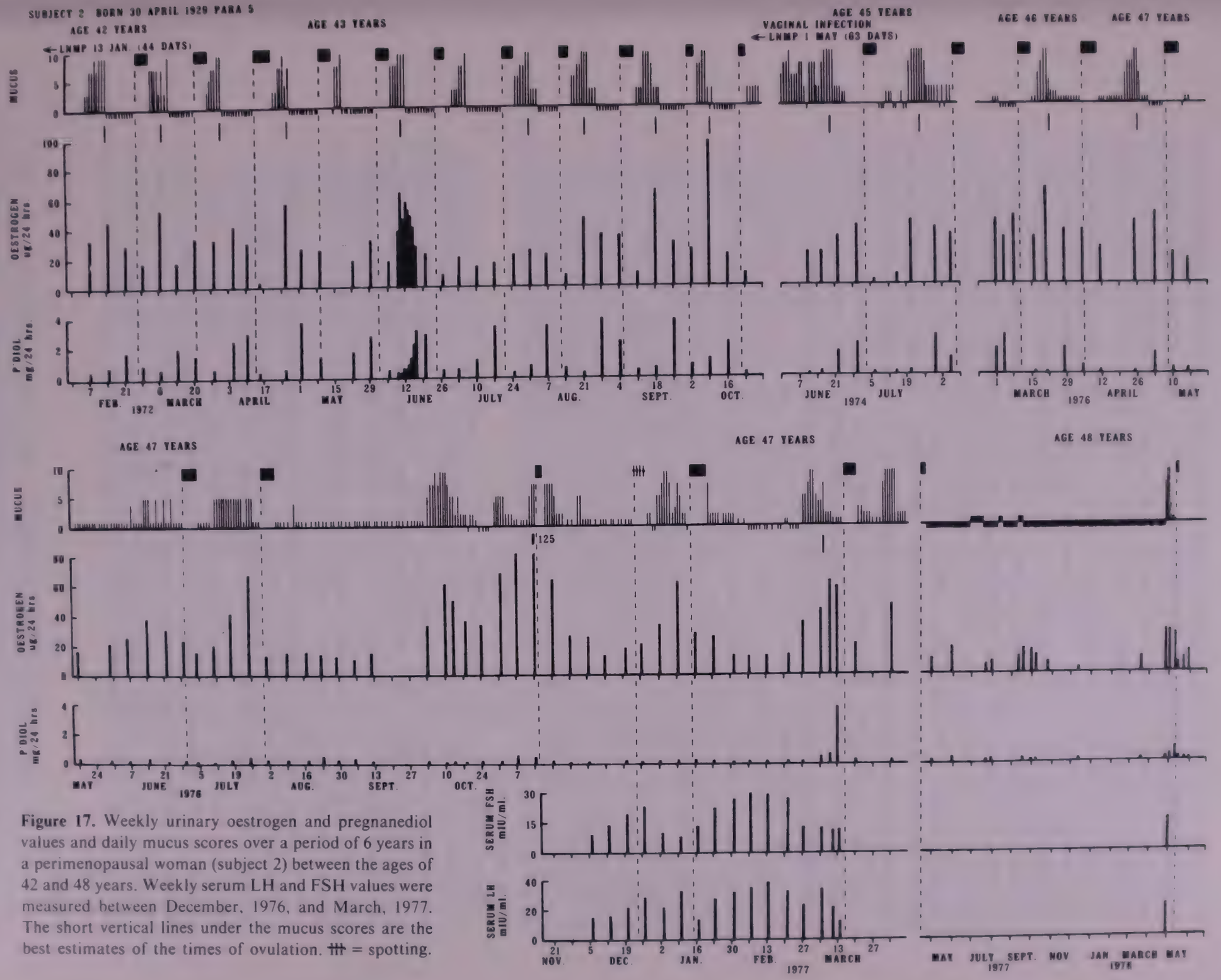

Figure 17. Weekly urinary oestrogen and pregnanediol values and daily mucus scores over a period of 6 years in a perimenopausal woman (subject 2) between the ages of 42 and 48 years. Weekly serum LH and FSH values were measured between December, 1976, and March, 1977. The short vertical lines under the mucus scores are the best estimates of the times of ovulation. ⫴ = spotting.

Subject 2 (Figure 17) was aged 43 years at the beginning of the study and had just recorded an unusually long cycle of 44 days which proved to be ovulatory. Regular ovulatory cycles were recorded during the next 9 months, with cycle lengths of 21–27 days and luteal phase lengths of 12–14 days. The mucus symptoms corresponded perfectly with the hormone patterns. The subject collected again in June and July, 1974, at the age of 45 years, during another long cycle when her mucus symptoms were being obscured by a vaginal infection. Two ovulatory cycles were identified. Collections recommenced in March, 1976, at the age of 46 years and were continued for 26 months. The first cycle was ovulatory, with pregnanediol values reaching 2·7 mg/24 hours, but during the next two cycles the luteal phase pregnanediol values began to decrease, the maximum value recorded in the March cycle being 1·8 mg/24 hours, and 1·4 mg/24 hours in the April cycle. Thereafter, the pregnanediol values remained low, in the range of 0·2–0·4 mg/24 hours, and a series of anovulatory cycles was recorded, lasting from between 3 and 15 weeks, with peak oestrogen values ranging from 40 to 125 μg/24 hours. These events are the reverse of the sequence seen with the establishment of ovulation in the girls after menarche (Figure 10). A small rise in the pregnanediol values to 0·7 mg/24 hours was seen before the bleed in November. Bleeding and spotting were occurring both as oestrogen breakthrough and withdrawal phenomena over this time. A rise in pregnanediol excretion to 3·9 mg/24 hours was observed in March, 1977, and indicated the first ovulatory episode for nearly a year. However, the luteal phase of this cycle lasted for only 8 days. During the next year episodes of cyclic ovarian activity were recorded, with oestrogen values which remained below 20 μg/24 hours. Amenorrhoea persisted throughout this time. In May, 1978, increased ovarian activity was again observed, the oestrogen values rising to 28 μg/24 hours and the pregnanediol values to 1 mg/24 hours. This activity was followed by 2 days of bleeding. At the end of July, 1978, the oestrogen values rose to 37 μg/24 hours and this was associated with fertile-type mucus; slight spotting occurred in August. The study continues.

Serum FSH and LH were measured weekly from December, 1977, to March, 1978. The FSH values were fluctuating between high normal menstrual cycle levels and post-menopausal levels, the fluctuations being the exact inverse of the oestrogen values. The LH values fluctuated in parallel with the FSH values, except for two subsidiary rises which occurred at the times of the peak oestrogen values, presumably representing surges in LH at these times. Such fluctuations in FSH and LH values are a common finding in climacteric women.

Throughout the study, subject 2 recorded mucus symptoms which corresponded exactly with the hormone values without exception. The last possibly fertile cycle occurred in February–March, 1976, at the age of 46 years, and the ovarian activity which has occurred during the following 2½ years has been completely infertile as judged by the hormone patterns. This subject recorded that hot flushes always denoted that the oestrogen values were low (less than 10 μg/24 hours) and that periods of purposeful activity and returning confidence corresponded with times of elevated oestrogen values. The total study of the 85 climacteric women supported these overall findings.

Conclusions

There is no doubt from the study that women who have been trained to interpret their mucus symptoms can thereby recognize with great accuracy the underlying cyclic changes in ovarian function which govern their fertility. It is obvious, too, that

this information is of great practical value in the achievement or avoidance of pregnancy. The study provides important information on ovarian activity under practically all circumstances which may be encountered during the reproductive lifetime of an individual. It provides information on the hormonal factors involved in the production of cervical mucus and in the initiation of uterine bleeding. This information, collected over a period of more than 15 years, has been extensively utilized in the continued refinements of the rules of the Ovulation Method (Billings) to the stage that it has reached today. As a corollary, the study has shown that do-it-yourself methods for directly measuring oestrogen and progesterone production, by urinary analyses, would be of considerable value, particularly to those women requiring reassurance in the recognition of their mucus patterns. The information expected from such methods and the performance required have been defined by the present study and development of assay methods is proceeding. A method has been developed for measuring urinary pregnanediol in the first instance, and is under trial, but it does not appear to be simple enough for universal use. Other studies have been conducted elsewhere on the user-effectiveness of the Ovulation Method (Billings).

Acknowledgments

We thank the many women, mainly NFP users, who documented their symptoms and contributed the many thousands of urine and blood samples which made this study possible. The information obtained also provides the normal data base necessary for our current studies on hormonal factors involved in the aetiology of breast and uterine cancers and of mood changes. We thank St. Vincent's Hospital Fertility Research Fund and the Ovulation Method Research and Reference Centre of Australia and the University of Melbourne for financial support.

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